REMARKS

Status of the Present Application

This Amendment is being submitted in response to the Office Action mailed on June 21, 2006. In the Office Action, the Examiner states that the following rejections have been withdrawn: (1) the rejection of claims 17-18 under 35 U.S.C. Section 102(e) in view of Wittwer et al.; (2) the rejection of claims 38-40 under 35 U.S.C. Section 102(b) in view of Meyer et al.; and (c) the rejection of claim 41 under 35 U.S.C. Section 103(a) as being obvious over Meyer et al. in view of Wittwer et al. Applicants thank the Examiner for removing each of the above-described rejections.

In the present Office Action, the Examiner has rejected the claims on new grounds which will be addressed in more detail herein. While not agreeing with the Examiner's rejections, Applicants make the amendments submitted herein in an effort to expedite prosecution.

Claim Amendments

Currently, claims 17, 18, 38-40 and 43-47 are pending. Claim 17 has been amended to remove the word "PCR" as the primers to be used in the methods of the present invention are not limited to solely PCR primers. Claim 38 has been amended to recite "to form a reaction mixture" in step a) so as to provide proper antecedent basis for the phrase "reaction mixture" in step b). Claim 41 previously recited that the method of claim 38 used the amplification conditions of claim 17. Claim 41 has been deleted. In its place, claims 44-47 have been added. Claims 44-47 recite additional amplification reagents and the amplification conditions to be performed in step b) of claim 38. Support for new claims 44-47 can be found in the specification on pages 6, lines 14-29 and page 7, line 18 through page 8, line 25. No new matter has been added as a result of the amendments to claims 17 and 38 or the addition of new claims 44-47.

Rejection of Claim 41 Under 35 U.S.C. Section 112

Claim 41 is rejected under 35 U.S.C. Section 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner says that claim 41 is unclear because while the claim provides for the use of the amplification conditions of claim 17, the claim fails to set forth any steps involved in the method. Applicants respectfully traverse this rejection.

Applicants have deleted claim 41 to expedite prosecution. Claims 44-47 have been added in view of the deletion of claim 41. Claims 44 and 46 do not recite the use of the amplification conditions of claim 17. Claims 45 and 47 specifically recite the amplification conditions to be performed in step b) of claim 38. Applicants submit that new claims 44-47 are clear and definite. Thereupon, in view of the deletion of claim 41, Applicants submit that this rejection is now moot and should be withdrawn.

Rejection of Claim 41 Under 35 U.S.C. Section 101

Claim 41 has also been rejected under 35 U.S.C. Section 101. Specifically, the Examiner says that even though this claim recites a use, this claim fails to set forth any steps that are involved in a method. Thereupon, this claim is an improper method claim. Applicants respectfully traverse this rejection.

As mentioned previously herein, claim 41 has been deleted. Claims 44-47 have been added in view of the deletion of claim 41. Applicants submit that new claims 44-47 recite steps that are involved in the method and thus are proper method claims. Thereupon, claims 44-47 fulfill the requirements of 35 U.S.C. Section 101. Finally, in view of the deletion of claim 41, Applicants submit that this rejection is now moot and should be withdrawn.

Rejection of Claims 38-40 and 43 Under 35 U.S.C. Section 102(b)

Claims 38-40 and 43 are rejected under 35 U.S.C. Section 102(b) as being anticipated by Evans et al., *J. Clin. Invest.,* 91:2150-2154 (1993) (hereinafter "Evans et al."). According to the Examiner, Evans et al. teach the method of claim 38. Specifically, the Examiner says that Evans et al. teach a method for detecting a target nucleic acid sequence suspected of having a single or larger deletion or insertion in a test sample that involves the steps of:

(a) contacting the test sample with amplification reagents comprising amplification primer (the Examiner refers to page 2151, paragraphs 1-2 of Evans et al.);

(b) subjecting the reaction mixture to amplification conditions to form a target nucleic acid sequence amplification product (the Examiner refers to page 2151, paragraph 2 of Evans et al.);

(c and d) detecting a first and second signal corresponding to a deletion and a standard nucleic acid (wild type amplification product) (the Examiner refers to page 2151, col. 2, Fig. 1, paragraph 1 of Evans et al.); and

(e) comparing the first and second signals in order to determine whether a deletion or insertion of at least 50 base pairs is present in the DNA in the test sample (the Examiner refers to Fig. 1 of Evans et al.).

In support of her rejection of claims 39-40 and 43, the Examiner refers to page 2151, col. 1, paragraphs 2-3 and Fig. 1 of Evans et al. which the Examiner asserts teach a deletion of 11.5 kb and that the deletion is in the *CYP2D6* locus, which is polymorphic. Applicants respectfully traverse this rejection.

Applicants submit that the Examiner has misinterpreted Evans et al. On page 2150, Evans et al., in describing CYP2D6, discuss that deficient CYP2D6 activity in poor metabolizers is caused by one of several gene defects, namely, gene deletion or point mutations/nucleotide changes. Evans et al. go on to state that "[I]n Caucasians, two prevalent inactivating mutations in the CYP2D6 gene (CYP2D6) are a point-mutation at the 3' splice site consensus sequence of intron 3 (CYP2D6(B) mutation), and a single nucleotide (adenine) deletion in exon 5 (CYP2D6(A) mutation) (10-12). Either of these mutations lead to defective mRNA and protein (9), and a deficiency in CYP2D6 activity. A third variant of the CYP2D6 locus leading to the absence of CYP2D6 activity, is a complete deletion of the CYP2D6 gene (13), which is detectable by RFLP analysis (11.5-kb XbaI restriction fragment) (14)." (See Evans et al., page 2150, right hand column).

On page 2151 in their description of the Methods, Evans et al. describe how for the identification of the CYP2D6(A) and CYP2D6(B) mutations, mutation-specific PCR amplification was performed. Primers, but no probes, were used during the PCR amplification (See, page 2151 of Evans et al., second full paragraph in the left hand column). For identification of a complete deletion of

the CYP2D6 gene, RFLP analysis was performed. Briefly, DNA was digested to completion with a XbaI restriction endonuclease and then subjected to agarose gel electrophoresis. Southern blotting was performed and a labeled cDNA probe was used. The presence of a band at 11.5 kb was used to identify the deleted gene (See, page 2151 of Evans et al., third full paragraph in the left hand column for the specific details of the RFLP analysis). Figure 1 on page 2151 of Evans et al. shows the results of the mutation-specific PCR amplification for the CYP2D6(A) and CYP2D6(B) mutations. The last line of Figure 1 says "RFLP analysis is required to identify the complete deletion of CYP2D6, the third major inactivating mutation at the CYP2D6 locus."

Claim 38 is directed to a method for determining whether a deletion or insertion of at least 50 base pairs is present in DNA in a test sample. The method involves:

(a) containing the test sample with amplification reagents to form a reaction mixture, wherein the amplification reagents comprise amplification primers;

(b) subjecting the reaction mixture to amplification conditions to form a target nucleic acid sequence amplification product, if the target nucleic acid is present in the test sample, and a standard nucleic acid amplification product;

(c) detecting a first signal that is proportional to the amount of the target nucleic acid sequence amplification product;

(d) detecting a second signal that is proportional to the amount of the standard nucleic acid amplification product; and

(e) comparing the first signal to the second signal to determine whether a deletion or insertion of at least 50 base pairs is present in the DNA in the test sample, wherein the amplification reagents comprise one primer that hybridizes to both the target nucleic acid sequence and the standard nucleic acid sequence.

The method of claim 38 is simply not disclosed by Evans et al. As discussed above, Evans et al. describe two (2) methods for detecting gene defects in the CYP2D6 gene. In the first method, point-mutations and single nucleotide changes are identified using mutation-specific PCR amplification. This mutation-specific PCR amplification involves two consecutive amplification reactions. For both the CYP2D6(A) and CYP2D6(B) mutations, the first amplification reaction isolates the "appropriate" segment of CYP2D6.

As mentioned above, the method of Evans et al. requires performing two separate amplification reactions with two different reaction mixtures to determine the presence of a mutation. In contrast, Applicants' method is performed once using a single reaction mixture. Moreover, the mutation-specific PCR amplification described by Evans et al. is used to detect point and single nucleotide mutations, not mutations which comprise deletions or insertions of at least 50 base pairs as is recited in claim 38.

In the second method, RFLP analysis is used for the identification of a CYP2D6 gene deletion. The RFLP analysis described by Evans et al., while employing a probe, does not employ any primers (no mention is made of the use of any PCR-RFLP analysis). More specifically, the cDNA probe is labeled with a radioactive isotope (^{32}P) by nick translation. This labeled probe is then hybridized to previously digested DNA and the restriction fragment length patterns examined after the film was exposed under the appropriate conditions. The 11.5 kb fragment referred to by the Examiner is identified using this RFLP analysis.

The RFLP analysis described above in Evans et al. for use in identifying the CYP2D6 gene deletion is not an amplification method. The method of claim 38 employs amplification. Specifically, claim 38 recites the use of "amplification reagents" which comprise "one primer that hybridizes to both the target nucleic

acid sequence and the standard nucleic acid sequence" and then subjecting a "reaction mixture to amplification conditions to form a target nucleic acid sequence amplification product". Therefore, the RFLP analysis described by Evans et al. for identification of a CYP2D6 gene deletion does not anticipate claim 38.

Therefore, because Evans et al. do not disclose each and every element of claim 38, Applicants submit that the rejection of claims 38-40 and 43 under 35 U.S.C. Section 102(e) in view of Evans et al. should be withdrawn.

Rejection of Claim 41 Under 35 U.S.C. Section 103(a)

Claim 41 is rejected under 35 U.S.C. 103(a) as unpatentable over Evans et al. in view of Van Ness et al. (U.S. Patent No. 6,361,940). According to the Examiner, Van Ness et al. teach a method for detecting a target nucleic acid sequence (CYP2D6) in a test sample comprising PCR thermal cycling conditions comprising:

(i) maintaining the reaction temperature for a time and temperature above 90°C sufficient to dissociate double stranded nucleic acid sequences (denaturation at 94°C for 30 sec);

(ii) maintaining the reaction mixture for a time and at a temperature from 45 to 65 °C to allow primers to hybridize to the target nucleic acid (annealing temperature 62 °C for 30 sec);

(iii) maintaining the reaction mixture for a time and at a temperature at least above the temperature in (ii) (68°C for 4 min + 20 sec/cycle);

(iv) raising the temperature of the reaction mixture to a temperature sufficient to activate the polymerase (68°C for 10 min) and repeatedly performing cycles to form an amplification product (repeated for 20 cycles) (The Examiner refers to column 98, line 55-65 of Van Ness et al.).

The Examiner says that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time that the invention was made to combine the method of amplification of a target nucleic acid as taught by Evans et al. with the step of PCR amplification cycles taught by Van Ness et al. to achieve the expected advantage of developing a sensitive and enhanced method for amplification of a specific target. Furthermore, the Examiner says that a person of ordinary skill in the art would have had a reasonable expectation of success that the modification of the method taught by Evans et al. with the thermal cycle steps taught by Van Ness et al. would result in the identification of both wildtype and mutant alleles in target nucleic acid. In view of this, the Examiner believes that one of ordinary skill in the art would have been "motivated to combine the methods of Evans et al. with the inclusion of thermal cycles as taught by Van Ness et al. to develop a sensitive and enhanced method for identifying both wildtype and mutant alleles in a single reaction" (See, Office Action, pages 6-7). Applicants respectfully traverse this rejection.

As discussed previously herein, claim 41 has been canceled. Claims 44-47 have been added in response to the deletion of claim 41. Claims 44 and 46 are dependent upon claim 38 and claims 45 and 47 are dependent upon claims 44 and 46, respectively.

The deficiencies of Evans et al. are discussed *supra*. Applicants' arguments are incorporated herein. The deficiencies of Evans et al. are not cured by Van Ness et al. Van Ness et al. disclose compositions and methods for increasing the specificity of a probe nucleic acid for a target nucleic acid in a hybridization solution. Specifically, Van Ness et al. disclose compositions that change the enthalpy of a nucleic acid duplex. As discussed previously, the Examiner refers to column 98, lines 55-65 of Van Ness et al. This section of Van Ness et al. relates to a P4502D6 validation assay. In line 55, Van Ness et al. describe how primers that flank the 2D6 gene were used to amplify a 4,681 base

pair genomic DNA fragment containing all of the relevant gene sequence. This section of Van Ness et al. does not disclose or suggest detecting any deletion or insertion of at least 50 base pairs in a test sample. In addition, the PCR reaction described by Van Ness et al. while employing primers, did not use any probes. The thermocycling conditions employed by Van Ness et al. were 94°C for 3 minutes; 10 cycles of 94°C for 30 seconds, 62°C for 30 seconds, 68°C for 4 minutes; 20 cycles of 94°C for 30 seconds, 62°C for 30 seconds, and 68°C for 4 minutes + 20 seconds/cycle; 68°C for 10 minutes (See Van Ness et al., column 98, lines 61-65).

Moreover, Applicants submit that the cycle steps described by Van Ness et al. are different than the cycle steps claimed in steps b-i) to b-iv) of claim 47. As discussed above, the method of Van Ness et al. does not employ any probes. Thereupon, because the method of Van Ness et al. does not employ probes, Van Ness et al. do not disclose or suggest maintaining the reaction mixture for a time and at a temperature at least 1°C above the temperature in step b-ii) sufficient to dissociate the probe hybrids (in the event that the probe is not completely complementary to the nucleic acid). To further illustrate the difference between the steps of the cycle of the present invention and the steps of the cycle disclosed by Van Ness et al., a comparison between the steps of the two cycles is provided for below in Table 1.

Table 1

Cycle steps recited in claim 17	**Van Ness et al. in column 98, lines 61-65 describes 10 cycles of:**	**The 10 cycles in Van Ness et al. are then followed by 20 cycles of:**
(i) maintaining the reaction mixture for a time and a temperature above 90°C sufficient to dissociate double	(i) 94°C for 30 seconds (note that prior to this step that the machine is allowed to come up to a temperature of 94°C for	(i) 94°C for 30 seconds

stranded nucleic acid sequences;	3 minutes)	
(ii) maintaining the reaction mixture for a time and at a temperature of from about 45°C to 65°C to allow the PCR primers and probe to hybridize to the nucleic acid and thereby form primer hybrids and probe hybrids;	(ii) 62°C for 30 seconds	(ii) 62°C for 30 seconds
(iii) maintaining the reaction mixture for a time and at a temperature at least 1°C above the temperature in (ii), sufficient to dissociate the probe hybrids, if the probe is not completely complementary to the nucleic acid; and		
(iv) raising the temperature of the reaction mixture to a temperature sufficient to activate the polymerase.[1]	(iii) 68°C for 4 minutes.	(iii) 68°C for 4 minutes + 20 seconds/cycle
		(iv) 68°C for 10 minutes.

As mentioned above, Van Ness et al. do not employ any probes and therefore do not disclose or suggest a separate step b-iii) in their cycle. Applicants submit that the step performed by Van Ness et al. at 68 °C for 4 minutes or for 4 minutes + 20 seconds/cycle is where the temperature of the reaction mixture is raised to a temperature sufficient to activate the polymerase. Applicants submit that the reason the reaction was maintained at 68 °C for 10 minutes was to provide the polymerase with additional time to finish incomplete duplexes so that a clean band could be observed on the gel.

[1] The specification on page 6, lines 28-29 states that a temperature sufficient to activate polymerases is typically between 60°C and 90°C, but are "most typically thought to be optimally active at 72°C".

Thereupon, in view of the deletion of claim 41, Applicants submit that this rejection is now moot and should be withdrawn. Additionally, there is absolutely nothing in Evans et al. and Van Ness et al. that discloses or suggests the methods of claims 44-47. Therefore, Applicants submit that claims 44-47 are not obvious under 35 U.S.C. 103(a) over Evans et al. in view of Van Ness et al.

Rejection of Claims 17-18 Under 35 U.S.C. Section 103(a)

Claims 17-18 are rejected under 35 U.S.C. Section 103(a) as being unpatentable over Evans et al. in view of Van Ness et al. (U.S. Patent No. 6,361,940) and Wittwer et al. (U.S. Patent No. 6,232,079). According to the Examiner, Evans et al. in view of Van Ness et al. teach a method for detecting a target nucleic acid sequence suspected of having a single or large deletion or insertion as discussed previously in this Office Action. The Examiner admits that neither Evans et al. nor Van Ness et al. teach the use of a probe in an amplification reaction.

With respect to Wittwer et al., the Examiner states that Wittwer et al. teach a method for monitoring hybridization during PCR for detecting a target nucleic acid sequence in a test sample, comprising:

(a) contacting the test sample with amplification reagents comprising a polymerase, a PCR primer pair, and a probe (the Examiner refers to column 6, lines 1-15, column 44, lines 24-38 of Wittwer et al.);

(b) performing PCR cycles (i) raising temperature to dissociate the double-stranded genomic DNA, (ii) lowering the temperature to allow primers and probe to hybridize to the target nucleic acid, (iii and iv) raising the temperature to dissociate the target-probe hybrids and extending the primers and continuously raising the temperature to permit temperature dependent polymerase extension

(the Examiner refers to column 44, lines 50-67, column 45, lines 1-12 of Wittwer et al.);

(c) repeatedly performing the PCR cycles to form an amplification product (the Examiner refers to column 45, lines 13-53 of Wittwer et al.); and

(d) detection of the amplification product as an indication of the presence of the nucleic acid (the Examiner refers to column 45, lines 13-53).

According to the Examiner, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the method of amplification of a target nucleic acid as taught by Evans et al. in view of Van Ness et al. with the step of primer extension in the presence of a probe or monitoring hybridization during PCR as taught by Wittwer et al. to achieve the expected advantage of developing a sensitive and enhanced method for amplification of a specific target. According to the Examiner, one of ordinary skill in the art would have had a reasonable expectation of success that the modification of the method taught by Evans et al. in view of Van Ness et al. with the step of monitoring hybridization during PCR would result in continuously monitoring of DNA amplification, identification and quantitation of nucleic acid and reducing laborious processing steps after PCR to identify the target nucleic acid (the Examiner refers to column 3, lines 14-33 of Wittwer et al.). The Examiner concludes by saying that "[T]herefore, an ordinary practitioner would have been motivated to combine the method of Evans et al. in view of Van Ness et al. with the inclusion of step [sic] of monitoring hybridization during PCR as taught by Wittwer et al. to develop a sensitive and enhanced method for amplification and quantitation of a specific target nucleic acid." (See, Office Action, page 8). Applicants respectfully traverse this rejection.

Evans et al. has been discussed previously herein and that discussion is herein incorporated by reference. The method of claims 17 and 18 are simply not disclosed or suggested by Evans et al. As discussed previously herein,

Evans et al. describe two (2) methods for detecting gene defects in the *CYP2D6* gene. In the first method, point-mutations and single nucleotide changes are identified using mutation-specific PCR amplification. This mutation-specific PCR amplification involves two consecutive amplification reactions. For both the *CYP2D6(A)* and *CYP2D6(B)* mutations, the first amplification reaction isolates the "appropriate" segment of *CYP2D6*. The second amplification reaction amplifies only the wild type sequence or the mutant sequence. As also previously discussed herein, Evans et al. requires performing two separate amplification reactions with two different reaction mixtures to determine the presence of a mutation. In contrast, Applicants' method is performed only once using a single reaction mixture.

Moreover, as recognized by the Examiner, the method of Evans et al. does not employ any probes. Thereupon, because the method of Evans et al. does not employ any probes, Evans et al. do not disclose or suggest maintaining the reaction mixture for a time and at a temperature at least 1°C above the temperature in step b-ii) sufficient to dissociate the probe hybrids (in the event that the probe is not completely complementary to the nucleic acid).

In the second method, RFLP analysis is used for the identification of a *CYP2D6* gene deletion. As mentioned previously above, RFLP analysis is not an amplification method. Therefore, this method is not relevant to the methods of claims 17 and 18 which involve the use of a primer pair and performing a cycle comprising the steps of: (i) maintaining the reaction mixture for a time and at temperature above 90°C, sufficient to dissociate double stranded nucleic acid sequences, (ii) maintaining the reaction mixture for a time and at a temperature from 45°C to 65°C to allow the PCR primers and probe to hybridize to the nucleic acid and thereby form primer hybrids and probe hybrids, (iii) maintaining the reaction mixture for a time and at a temperature at least 1°C above the temperature in (ii), sufficient to dissociate the probe hybrids, if the probe is not

completely complementary to the nucleic acid, and (iv) raising the temperature of the reaction mixture to a temperature sufficient to activate the polymerase.

The deficiencies of Evans et al. are not cured by Van Ness et al. and Wittwer et al. As discussed previously herein, Van Ness et al. do not disclose or suggest detecting any single or large deletions or insertions in a test sample. In addition, the PCR reaction described by Van Ness et al. while employing primers, did not use any probes.

As also previously discussed herein, Applicants submit that the cycle steps described by Van Ness et al. are different than the cycle steps claimed in steps b-i) to b-iv) of claim 17. As discussed above, the method of Van Ness et al. does not employ any probes. Thereupon, because the method of Van Ness et al. does not employ probes, Van Ness et al. do not disclose or suggest maintaining the reaction mixture for a time and at a temperature at least 1°C above the temperature in step b-ii) sufficient to dissociate the probe hybrids (in the event that the probe is not completely complementary to the nucleic acid). This is exemplified in the comparison between the steps of the two cycles that is provided for in Table 1.

The deficiencies of Evans et al. and Van Ness et al. are not cured by Wittwer et al. As discussed in Applicants' Amendment filed on January 13, 2006, Wittwer et al. in column 21, lines 22-32, disclose that amplification yields and product specification were optimal when denaturation (93 °C) and annealing (55 °C) were less than 1 second and that no advantage was found for longer denaturation or annealing times. Wittwer et al. also teach that yield increased with longer elongation times at 77 °C, but that there was little change with elongation times longer than 10-20 seconds. In column 44, lines 50-62, Wittwer et al. describe cycling conditions where denaturation was performed at 94 °C for 0 seconds, annealing was performed at 50 °C for 10 seconds and extension was

performed at 72 °C for 0 seconds. This cycle was then repeated 50 times and then cooled to 45 °C.

The cycle steps described by Wittwer et al. are different than the cycle steps claimed in steps b-i) to b-iv) of Applicants' method. The difference between the steps of each of the cycles is specifically shown below in Table 2.

Table 2

Cycle steps recited in claim 17	**Cycle steps described by Wittwer et al. in column 44, lines 50-62**
(i) maintaining the reaction mixture for a time and a temperature above 90°C sufficient to dissociate double stranded nucleic acid sequences;	(i) denaturation was performed at 94°C for 0 seconds
(ii) maintaining the reaction mixture for a time and at a temperature of from about 45°C to 65°C to allow the PCR primers and probe to hybridize to the nucleic acid and thereby form primer hybrids and probe hybrids;	(ii) annealing was performed at 50°C for 10 seconds
(iii) maintaining the reaction mixture for a time and at a temperature at least 1°C above the temperature in (ii), sufficient to dissociate the probe hybrids, if the probe is not completely complementary to the nucleic acid; and	
(iv) raising the temperature of the reaction mixture to a temperature sufficient to activate the polymerase.[2]	(iii) extension was performed at 72°C for 0 seconds.

In claim 17, in step b-iii), the reaction mixture is maintained for a time and at a temperature at least 1°C above the temperature in step b-ii) sufficient to dissociate the probe hybrids if the probe is not completely complementary to the

[2] The specification on page 6, lines 28-29 states that a temperature sufficient to activate polymerases is typically between 60°C and 90°C, but are "most typically thought to be optimally active at 72°C".

nucleic acid (such a probe would be considered to be a "mismatched" probe). Likewise, probe hybrids that are completely complementary to the nucleic acid will not dissociate (such a probe would be considered to be a "matched" probe). Once this step is completed, the temperature of the reaction mixture is raised to a temperature sufficient to activate the polymerase (step b-iv)) and to allow for extension.

In contrast, Wittwer et al. do not disclose or suggest a separate step b-iii) in their cycle. Rather, after annealing is performed at 50°C, the temperature of the reaction mixture is immediately raised to 72°C to activate the polymerase and to allow for extension. Thereupon, Wittwer et al. teach the simultaneous dissociation of a mismatched probe and polymerase activation. As shown above in Table 2, in Applicants' method, these cycle steps are separated into two separate steps that are performed under different reaction conditions (namely, at a certain temperature for a certain amount of time). Also, as discussed in Applicants' Amendment filed on January 13, 2006, the performance of each of the steps b-i) to b-iv) has been found to improve the resolution of the method particularly when compared to the three step cycle methods of the prior art, such as Wittwer et al. (See the second and third experiments in Paragraphs 5 and 6 of the Declaration of Maria C. Gentile Under 37 C.F.R. Section 1.132 filed in the Amendment filed on January 13, 2006).

As demonstrated by the arguments above, there is absolutely nothing in Evans et al., Van Ness et al. and Wittwer et al. that disclose or suggest Applicants' claimed method. Thereupon, Applicants submit that the rejection of claims 17 and 18 under 35 U.S.C. Section 103(a) as being obvious in view of Evans et al., Van Ness et al. and Wittwer et al. should be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. Sections 112, 101, 102 and 103. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Should the Examiner have any questions concerning the above, she is respectfully requested to contact the undersigned at the telephone number listed below. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

If any additional fees are incurred as a result of the filing of this paper, authorization is given to charge deposit account no. 23-0785.

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